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Genetic Modifiers of Cognitive Maintenance Among Older Adults

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Abstract: *Objective:* Identify genetic factors associated with cognitive maintenance in late life and assess their association with gray matter (GM) volume in brain networks affected in aging. *Methods:* We conducted a genome-wide association study of ~2.4 M markers to identify modifiers of cognitive trajectories in Caucasian participants ($N = 7{,}328$) from two population-based cohorts of non-demented elderly. Standardized measures of global cognitive function (*z*-scores) over 10 and 6 years were calculated among participants and mixed model regression was used to determine subject-specific cognitive slopes. "Cognitive maintenance" was defined as a change in slope of ≥ 0 and was compared with all cognitive decliners (slope < 0). In an independent cohort of cognitively normal older Caucasians adults ($N = 122$), top association findings were then used to create genetic scores to assess whether carrying more cognitive maintenance alleles was associated with greater GM volume in specific brain networks using voxel-based morphometry. *Results:* The most significant association was on chromosome 11 (rs7109806, $P = 7.8 \times 10^{-8}$) near *RIC3*. RIC3 modulates activity of α7 nicotinic acetylcholine receptors, which have been implicated in synaptic plasticity and beta-amyloid binding. In the neuroimaging cohort, carrying more cognitive maintenance alleles was associated with greater volume in the right executive control network (RECN; $P_{FWE} = 0.01$). *Conclusions:* These findings suggest that there may be genetic loci that promote healthy cognitive aging and

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that they may do so by conferring robustness to GM in the RECN. Future work is required to validate top candidate genes such as *RIC3* for involvement in cognitive maintenance. *Hum Brain Mapp 35:4556–4565, 2014.*

Key words: genetics; genomics; aging; cognition; genome wide association study; neuroimaging

INTRODUCTION

Although significant research has gone into understanding the risk factors and pathological processes of dementias, little is known about factors contributing to cognitive maintenance throughout aging. It has been suggested that maintenance of cognitive ability over time involves adaptive changes that compensate for deficits such as reduced synaptic plasticity [Blau et al., 2011], which naturally occur with aging [Mauceri et al., 2011; Raz and Rodrigue, 2006]. Factors that globally impact cognition may provide an alternate therapeutic approach for treating dementia, for which genetic heterogeneity and environmental risk factors may be further complicating risk factors [Lee and Silva, 2009].

The emerging field of imaging genomics provides an innovative way to identify brain phenotypes associated with genetic variation [Thompson et al., 2010]. Direct assessment of the effect of genetic variation on the brain allows for logical interpretation of results as reflected in established brain–behavior relationships. We performed the first genome-wide association study (GWAS) to identify genetic modifiers of cognitive trajectory in healthy elderly men and women. Then, to directly assess the clinical relevance of candidate variants, we created genetic scores using the top 10 single nucleotide polymorphisms (SNPs) to test whether carrying more protective alleles was associated with greater gray matter (GM) volume in an independent group of cognitively normal older adults. We chose *a priori* to assess three regions of interest (ROIs) representing the functional networks subserving cognitive domains most affected in cognitive aging [Kaup et al., 2011]: the default mode network (DMN; memory retrieval), and the right and left executive control networks (RECN and LECN, respectively; executive function and working memory) [Montembeault et al., 2012; Tomasi and Volkow, 2012].

MATERIALS AND METHODS

Participants

Elderly GWAS participants were from two independent cohorts, the all-female Study of Osteoporotic Fractures (SOF) [Cummings et al., 1995] and the all-male Osteoporotic Fractures in Men (MrOS) [Blank et al., 2005; Orwoll et al., 2005] Study. SOF is a longitudinal epidemiologic study of 10,366 community-dwelling women age 65 years or older, recruited from four study centers located in: Baltimore, MD; Minneapolis, MN; Portland, OR; and the Monongahela Valley near Pittsburgh, PA. Exclusion criteria included a bilateral hip replacement or if women were unable to walk without assistance. The baseline SOF exams were conducted from 1986–1988, when 9,704 European American women were recruited [Cummings et al., 1995; Vogt et al., 2003]. Baseline examination for MrOS occurred from 2000 to 2002, during which 5,994 community-dwelling men 65 years or older were enrolled at six clinical centers in the United States: Birmingham, AL; Minneapolis, MN; Palo Alto, CA; the Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA [Blank et al., 2005; Orwoll et al., 2005]. To participate, men needed to be able to walk without assistance and must not have had a bilateral hip replacement. Individuals that were related to each other in SOF and MrOS were identified based on whole genome SNP data and only a single individual from the related pair was included in the analysis (the subject with non-missing phenotype data or, if both members of the related pair had non-missing phenotypes, the sample with the lowest SNP missing rate was retained).

Neuroimaging replication participants ($N = 122$ Caucasian individuals) were part of on-going healthy aging studies at the Memory and Aging Center (MAC) at the University of California, San Francisco (UCSF). Cognitively normal older adults were recruited through a variety of methods, primarily through newspaper advertisements and word-of-mouth and were required to have a knowledgeable informant. Cognitively normal older adults had MRI scans acquired within 1 year of clinical evaluation, were self-described Caucasian, and had genotypes available for analysis. Normal cognition was based on the absence of cognitive complaints from the participant and their informant, a normal neurological examination and clinical dementia rating scale sum of boxes score = 0 [Morris, 1993].

Standard Protocol Approvals, Registrations, and Patient Consents

All women from SOF provided written informed consent, and the institutional review board at each site approved the study. All men from MrOS provided written informed consent, and the institutional review board at each site approved the study. All MAC participants

provided written informed consent, and the UCSF institutional review board approved all aspects of this study.

Cognitive Assessment

In SOF, the shortened Mini-Mental State Exam (MMSE) [Folstein et al., 1975] with a maximum of 26 points was used to assess global cognitive ability and was administered at baseline, years 4, 6, and 10. In MrOS, the Modified MMSE (3MS) [Teng and Chui, 1987] was administered at baseline, years 4 and 6. A standard neuropsychological battery was performed in MAC participants as previously described [Rankin et al., 2005].

Genotype Acquisition and Quality Control

Genotyping for SOF, MrOS, and MAC participants was performed on the Illumina Omni1-Quad array genotyping platform as per manufacturer's instructions. Genotyping of SOF and MrOS samples was performed at the Broad Institute of Harvard and MIT and MAC samples were genotyped at the University of California Los Angeles. Imputation was performed in SOF and MrOS participants only for all individuals of European American genetic background (as determined by principal components analysis), using CEU HapMap Phase 2 data as reference. Of 3,020,488 HapMap Phase 2 imputed SNPs, there were a total of 2,457,365 SNPs available for meta-analysis (2,368,637 in SOF and 2,455,897 in MrOS) after excluding those with MAF < 0.01, Hardy–Weinberg Equilibrium (HWE) $P < 0.001$, call rate $< 95\%$ and imputation accuracy < 0.3. SNPs genotyped in the MAC cohort were similarly required to have MAF > 0.01, HWE $P > 0.001$, and call rate $> 95\%$ to be included in the genetic score.

Image Acquisition and Preprocessing

Structural images were acquired in MAC samples using previously described sequences [Sturm et al., 2013] on 3 T ($N = 103$) and 1.5 T ($N = 19$) scanners. T_1-weighted structural MR images were segmented in SPM8 running under Matlab then preprocessed with DARTEL [Ashburner, 2007] using previously described methods [Ashburner and Friston, 2000; Wilson et al., 2009]. DARTEL-processed GM images were then smoothed with an 8-mm kernel. Masks for each functional network ROI were from a previously published study (Supporting Information Fig. S1) [Habas et al., 2009].

Genetic Score

Genetic scores for imaging analysis in MAC samples were calculated using SNPs from the top 10 findings from the combined SOF-MrOS GWAS that had genotypes available in the MAC samples. We arbitrarily chose to survey the top 10 SNPs because they represented the strongest genomic candidate regions for cognitive maintenance. Only the most significantly associated SNP out of sets in strong linkage disequilibrium ($r^2 > 0.8$) were used for analysis so each independently associated region was represented once in the score. Scores were weighted by the beta value from the original GWAS (SOF or MrOS) with the strongest association *P*-value for the effect allele (MrOS for all three SNPs included in the final score). Genetic scoring was performed in PLINK [Purcell et al., 2007].

Statistical Analysis

Standardized measures of global cognitive function (*z*-scores) were calculated for MMSE (SOF) and 3MS (MrOS) repeated measures. Participant-specific slopes and intercepts for SOF and MrOS participants were calculated using mixed effect regression models (PROC MIXED in SAS, SAS Institute, Cary, NC). Mixed effect regression enables estimation of population-level fixed effects (overall rate of change in cognitive function in the entire sample) and individual-level random effects (individual deviation from the overall group pattern). Our models allow each participant to have a unique intercept and trajectory (change in cognitive function). Fixed effects included site, age and education. "Cognitive maintenance" was defined as a change in global cognitive function over time (slope) of ≥ 0.

GWAS of SOF and MrOS were performed in each cohort separately using logistic regression in R (v2.13.0) that corrected for population substructure with the first four principal components. Results were then combined via fixed effect meta-analysis with inverse variance weights and genomic control in METAL [Willer et al., 2010] and are presented as the final analysis. Heterogeneity between sexes was tested using GWAMA [Magi et al., 2010; Magi and Morris, 2010].

For VBM analysis, a voxel-wise general linear model (GLM) was conducted within each of the *a priori* defined ROIs (Supporting Information Fig. S1). The GLM modeled genetic score as a predictor of GM volume and included as nuisance variables age, total intracranial volume (TIV), sex, scan type (1.5 T or 3 T), education (years), handedness ($N = 107$ right, $N = 15$ left/ambidextrous) and number of *APOE* $\epsilon 4$ alleles (0 [$N = 91$], 1 [$N = 26$], or 2 [$N = 5$]). To adjust for multiple testing, 1,000 permutation analyses combining cluster peak intensity and extent were used [Hayasaka and Nichols, 2004]. Permutation analysis is a resampling approach that allows derivation of a study-specific error distribution from which the one-tailed T-threshold representing a family-wise error (FWE) correction of $P_{FWE} < 0.05$ can be established [Kimberg et al., 2007]. To quantify neuroimaging findings, mean GM proportion (a proxy of volume) was extracted for each cluster, summed across the ROI, and adjusted for the same nuisance variables included in the VBM linear model. Analysis was run using vlsm2.5 [Bates et al., 2003].

TABLE I. Top meta-analysis findings for cognitive maintenance from SOF and MrOS

SNP	Chr	BP	Nearest gene	A1	A2	MAF	Imp	HWE	*N*	Beta [SE][a]	*P* value
rs7109806[b]	11	8199205	*RIC3*	T	C	0.09	N	0.47	7,328	−0.75 [0.14]	7.80 E −08
rs6578942	11	8199746	*RIC3*	T	C	0.09	N	0.56	7,328	−0.72 [0.15]	7.96 E −08
rs2460141	15	74319900	*PML*	C	G	0.01	Y		3,820	−2.19 [0.43]	4.93 E −07
rs7814474	8	81222009	*TPD52*	C	G	0.04	Y		7,328	−0.97 [0.22]	1.81 E −06
rs7918950[b]	10	70678711	*DDX50*	A	G	0.22	Y		7,328	−0.54 [0.13]	2.17 E −06
rs9428707	1	236282325	*GPR137B*	A	C	0.01	Y		3,820	−1.71 [0.37]	3.13 E −06
rs2605578	11	92782276	*MTNR1B*	T	C	0.50	Y		7,328	−0.44 [0.10]	3.54 E −06
rs11020267[b]	11	92698003	*MTNR1B*	A	G	0.39	N	0.05	7,328	−0.36 [0.10]	4.11 E −06
rs11020270	11	92700892	*MTNR1B*	C	G	0.39	Y		7,328	−0.37 [0.10]	4.12 E −06
rs10831025	11	92696418	*MTNR1B*	T	C	0.39	N	0.07	7,328	−0.36 [0.10]	4.61 E −06

[a]Effect sizes are provided for the MrOS GWAS and were used to calculate the genetic scores. Chr—chromosome; BP—base position; A1—reference allele; A2—alternate allele; MAF—minor allele frequency for A2; imp—imputed SNP (Yes/No); HWE—Hardy-Weinberg Equilibrium *P*-value for genotyped SNP; *N*—total number of individuals available for meta-analysis of SOF + MrOS GWAS; Beta [SE]—beta ± standard error from MrOS GWAS.
[b]Indicates SNP was used to calculate the genetic score for VBM analysis.

RESULTS

A total of 3,508 women and 3,820 men had genetic data, ≥2 cognitive test scores available, and were of European ancestry and unrelated for inclusion in the GWAS analysis. Of the 3,508 SOF participants, 781 (22.3%) women were cognitive maintainers. Maintainers were around the same age as decliners (mean ± SD 71.3 ± 4.9 years versus 71.5 ± 5.4 years in decliners, $P = 0.25$), but tended to have lower education (12.0 ± 2.3 versus 12.8 ± 2.9 in decliners, $P < 0.0001$) and higher baseline MMSE scores (25.1 ± 1.2 versus 24.6 ± 1.7 in decliners, $P < 0.0001$). In MrOS, 222 (5.8%) of 3,820 men were cognitive maintainers and they tended to be older (75.5 ± 5.5 years versus 73.9 ± 6.0 years, $P = 0.002$), have lower education (61.7% versus 77.5% with greater than 12 years education, $P < 0.0001$) and higher baseline 3MS scores (95.1 ± 3.8 versus 93.5 ± 5.5, $P = 0.0002$).

Top ten findings from the SOF and MrOS combined GWAS identified six different genes/regions associated with cognitive maintenance (Table I). The most significant association was an intergenic SNP on chromosome 11, rs7109806 ($P = 7.8 \times 10^{-8}$), which nearly reached genome-wide significance ($P < 5 \times 10^{-8}$). Four of the top 10 SNPs were located within the coding region of *MTNR1B*, a high-affinity melanocortin receptor expressed primarily in brain and retina. Q–Q plots for the GWAS are shown in Supporting Information Figure S2.

To evaluate the clinical relevance of our top 10 cognitive maintenance GWAS findings, we created genetic scores representing "dose" of cognitive maintenance alleles and assessed their association with GM volume in an independent group of 122 cognitively normal older adults (MAC cohort: 68.9 ± 7.0 years old, 58.2% female, 17.3 ± 2.1 years of education). We were specifically interested in assessing whether carrying more cognitive maintenance alleles was associated with greater volume in functional networks underlying cognitive domains most vulnerable to aging. We arbitrarily chose to survey the top 10 SNPs for their clinical relevance. Three independent SNPs representing three of the six genes in the top 10 findings had been genotyped in the MAC cohort and were used to create the genetic score (SNPs included in the scoring are marked by[b] in Table I). Higher genetic score was significantly associated with greater GM volume in three regions of the RECN ($P_{FWE} = 0.01$–0.03, Fig. 1, Table II). A plot of the sum of the volume of these three RECN regions as a function of genetic score is shown in Supporting Information Figure S3. No regions in the DMN or regions in the LECN not overlapping with the RECN demonstrated any significant findings ($P_{raw} > 0.001$).

Using a simplified scoring scheme, we plotted the sum of the volumes of the three regions within the RECN as a function of the number of cognitive maintenance alleles to determine the average increase in GM volume with each "dose" of putative protective allele (Fig. 2). There were $N = 24$ with no alleles, $N = 35$ with one allele, $N = 38$ with two alleles, $N = 21$ with three alleles and $N = 4$ with four alleles. No individuals had more than four cognitive maintenance-associated alleles. After normalizing to volume in individuals with no maintenance alleles, we observed a dose-dependent effect with an average of 6% greater volume for each additional cognitive maintenance allele. Although the majority of individuals carried two protective alleles, individuals with three or four showed approximately 20%–25% greater volume, when compared to those with no alleles.

DISCUSSION

Our GWAS of cognitive maintenance in over 7,000 elderly, community-dwelling men and women yielded an association with variant rs7109806 with a *P*-value close to genome-wide significance. In an independent cohort, we

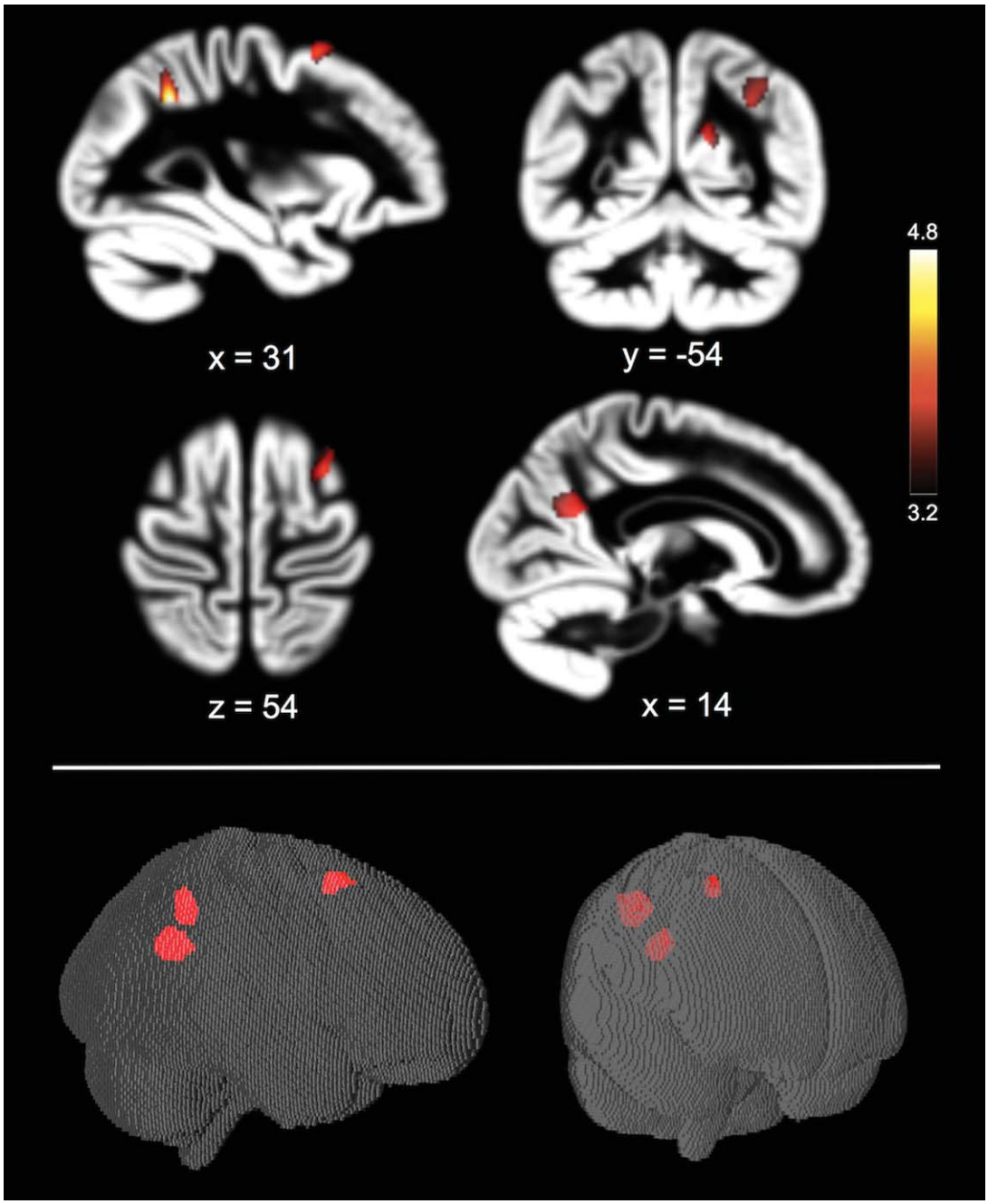

Figure 1.

Higher cognitive maintenance genetic scores are associated with greater GM volume in RECN. VBM T-map overlaid on slices of template used for image processing in MRIcron, thresholded at $P_{raw} < 0.001$. Images are in neurological orientation, with MNI coordinates provided below. 3D renders are visualized on a normal template brain in Connectome Workbench.

found that higher cognitive maintenance genetic scores derived from this and two other top 10 SNPs were associated with greater volume in the RECN, a functional network associated with working memory, attention and task control. By plotting volume of the RECN by number of cognitive maintenance allele, we observed a dose-dependent increase such that individuals with three alleles had an average of 20% greater volume compared to those

TABLE II. VBM findings

Region	Volume (mm^3)	Max *T*	*X*	*Y*	*Z*	P_{FWE}
Right precuneus	942	3.77	12	−55	22	0.01
Right angular gyrus	854	4.80	30	−51	34	0.01
Right middle frontal gyrus	381	3.87	30	8	54	0.03

Regions are annotated using the Anatomical Automatic Labeling atlas. Max *T*—maximum *T*-score for the cluster; *X*, *Y*, *Z*—Montreal Neurological Institute coordinates; P_{FWE}—family-wise error adjusted *P*-value.

with no alleles. This suggests that the effect of carrying alleles associated with cognitive maintenance may be quite significant.

Our top SNP is located between *RIC3* and *LMO1*. It is possible that this intergenic polymorphism affects a non-coding gene element such as a transcription factor binding site or enhancer, or that this variant alters epigenetic modification of the region. Alternatively, it may tag other, functional variants in a neighboring gene. *RIC3* is a tempting gene candidate; RIC3 modulates activity of nicotinic acetylcholine receptors (nAChRs), which have been implicated in synaptic plasticity. RIC3 enhances surface expression and functional properties of nAChRs, including the α7 subtype [Treinin, 2008] which has high affinity for amyloid beta (Aβ) 1–42 [Wang et al., 2000]. Aβ1–42 is a neurotoxic, self-associating peptide that contributes to formation of amyloid plaques in Alzheimer's disease (AD) [Lambert et al., 1998]. Four other genes in the top findings were previously implicated in other GWAS: *PML* in myopia [Meng et al., 2012], Paget's disease [Albagha et al., 2011], and height [Lango Allen et al., 2010]; *TPD52* in monoamine metabolite levels in cerebrospinal fluid [Luykx et al., 2013]; *GPR137B* in working memory in response to olanzapine treatment in schizophrenia [McClay et al., 2011]; *MTNR1B* for multiple metabolic- and glucose-related phenotypes (e.g., fasting glucose [Prokopenko et al., 2009]; metabolic traits [Sabatti et al., 2009]). In addition to *RIC3*, *MTNR1B* is a particularly intriguing candidate given the role metabolic syndrome may play in risk for cognitive decline [Arvanitakis et al., 2004; Baker et al., 2011; Panza et al., 2010; Yaffe, 2007a, b]. Further mapping studies will be required to assess these candidates for causative non-coding or gene variation in cognitive maintenance.

Genetic risk factors for AD such as *APOE* ϵ4 may also modify cognitive trajectories in healthy aging [Caselli et al., 2007, 2012; Sweet et al., 2012]. There were 123 SNPs associated with AD and its related phenotypes in the NHGRI Catalog of Published GWAS and representing the *APOE/TOMM40/APOC1* linkage block (19q13-q13.2 chromosomal region [Jun et al., 2012; Seripa et al., 2012]) also included in our analysis of cognitive maintenance. Of these, 12 had $P < 0.05$ in our GWAS. The lowest *P*-value was at rs4420638 ($P = 3.13 \times 10^{-5}$) that tags the *APOE/TOMM40/APOC1* region and was identified in a GWAS of AD risk in European ancestry individuals [Kamboh et al., 2012b]. Additional genes represented included *PVRL2* [Ramanan et al., 2013], *HRK*, *RNFT2* [Kamboh et al., 2012a], *DISC1* [Beecham et al., 2009], *POLN* [Logue et al., 2011], and *ZNF320* [Hollingworth et al., 2012]. However, there were 86 other SNPs in our analysis that demonstrated stronger associations with cognitive maintenance than the top AD SNP representing *APOE/TOMM40/APOC1*. This suggests that genetic variation associated with AD likely plays a lesser role in cognitive maintenance.

Our study benefited from a large cohort of well-characterized older adults who have been followed longitudinally, allowing for a sophisticated measure of cognitive maintenance over time. In addition, our novel research approach allowed us to directly assess the biological validity of our candidate SNPs in the context of a clinically oriented research study of healthy aging. We acknowledge that the use of a binary cutoff for cognitive maintenance may lead to misclassification of some subjects

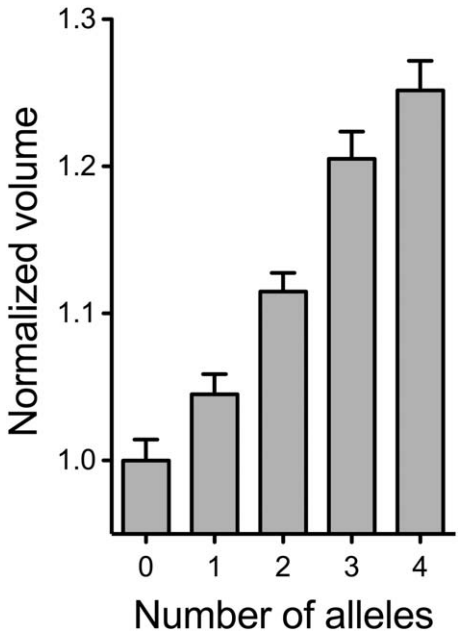

Figure 2.

Proportional increase in volume by number of cognitive maintenance alleles. Volume in RECN is shown by number of cognitive maintenance alleles, normalized to value for no alleles. Data is mean ± SE adjusted for age, sex, education, TIV, scan type, handedness, and *APOE* ϵ4 allele count.

based on their true underlying change. However, results ignoring misclassification errors in binary outcomes lead to attenuation of effect estimates and likely loss of power to detect true association findings [Neuhaus, 1999]. Use of frameworks incorporating imaging and genetic analysis into one model may provide better-powered analysis in future studies [Batmanghelich et al., 2013]. Other limitations of this study included having different proportions of cognitive maintainers in the SOF and MrOS cohorts and somewhat insensitive cognitive battery. Indeed, the proportion of cognitive maintainers was higher in the female SOF cohort. The top five associated SNPs analyzed in both cohorts demonstrated significant heterogeneity between sexes ($P < 0.05$); while effects in each cohort were always in the same direction, they were on average $\sim 2.5\times$ higher in MrOS versus SOF. This observation may represent a biological phenomenon, though it may also be a survival effect because the males were on average older than the females.

In this study, we used a genome-wide survey to identify candidate genes that may play a role in cognitive maintenance by promoting GM robustness in areas of the brain important for executive function. Taking an imaging genomics approach of assessing genetic scores derived from top GWAS findings for their association with GM volume may represent a clinically relevant measure of how genetic variation affects brain structure and, ultimately, function. We feel the strength of our GWAS findings and their ability to predict greater volume in brain regions important for cognitive domains vulnerable in aging [Hinman and Abraham, 2007] provide compelling evidence for a role in cognitive maintenance. Previous findings associating polygenic AD risk scores with cortical thickness in regions of the brain most affected in AD in healthy older adults [Sabuncu et al., 2012] further suggest these results are of clinical relevance. The use of composite genetic and imaging biomarkers improves predictions of AD progression [Filipovych et al., 2012] and suggests that complementary studies of cognitive maintenance genetic variants and anatomical correlates may be useful in identifying individuals most likely to experience successful cognitive aging. Similar to studies of brain regions affected in AD, multimodal studies of longitudinal change in RECN volume may also allow for identification of additional gene modifiers [Vounou et al., 2012] and functional pathways [Silver et al., 2012] that promote healthy cognition in aging. Future studies will be required to generalize these findings to diverse populations and to directly assess whether they have a modifying role in disease risk, trajectory, and outcome.

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